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(54) Title: IMPROVED SYNTHESIS OF RACEMIC SERTRALINE

(57) Abstract: The present invention describes an improved process for synthesis of sertraline, *cis*-(1S), (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine. The new compound N-R-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthaleneimine is hydrogenated to form N-R-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine which next is N-methylated to form N-R-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine. This latter compound is finally converted into sertraline by removal of the group R. The starting compound N-R-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthaleneimine can be obtained in high yield from 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone, tetralone, by reaction with R-amine. Further, new valuable intermediates for the synthesis of sertraline are provided.

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IMPROVED SYNTHESIS OF RACEMIC SERTRALINE

5 The present invention relates to a new improved process for producing cis-(1S), (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, hereinafter referred to as "sertraline", or salts thereof, and to new intermediates in the process.

10

BACKGROUND OF THE INVENTION

 Sertraline hydrochloride is a valuable
15 pharmaceutically active substance which is widely used for treatment of depressions and anxiety disorders.

 In DK 153 390 a process for the production of sertraline is described where a key intermediate 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone,
20 hereinafter referred to as "tetralone", is condensed with an amine having the formula HNR_1R_2 , wherein R_1 is hydrogen or n-alkyl with 1-3 carbon atoms, and R_2 is n-alkyl with 1-3 carbon atoms, in the presence of titanium tetrachloride to the corresponding N-methyl-
25 imine. Subsequently the N-methyl-imine is hydrogenated, using palladium on carbon as catalyst, to a mixture of cis and trans isomers of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine. The racemic cis-isomer is separated
30 from the trans-isomer by crystallisation of the cis-isomer as a hydrochloride from a methanol or ethanol solution. Finally the racemic cis-isomer is resolved by a diastereomeric crystallisation with D-(-)-mandelic acid in order to obtain the desired
35 stereoisomer cis-(1S), (4S)-N-methyl-4-(3,4-

dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, sertraline.

The cis/trans ratio obtained in the hydrogenation step is 70/30 which results in an overall yield of 68 % racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine.

WO 93/01161 describes a process for the production of trans-N-alkanoyl-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, from the corresponding 4-hydroxy precursor. EP 594 666 describes the formation of the cis-N-alkanoyl-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine by elimination and subsequent catalytic hydrogenation. Further EP 594 666 describes that the alkanoyl group can be removed to form cis isomer i.e. racemic sertraline.

In WO 98/27050 a process for the preparation of racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is described, wherein tetralone is reacted with N-methyl-hydroxylamine to produce N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-en-amine-N-oxide which is hydrogenated in the presence of a catalyst to form N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine. The cis isomer is separated by precipitation. A cis/trans ratio of 80/20 and an overall yield of 69 % racemic cis-isomer is obtained.

The above processes provide sertraline starting from tetralone. Tetralone may be produced in a 5-step process as described in DK 153 390, with benzoyl chloride as starting material.

DK 171 020 describes a procedure where an α -naphthol is reacted with ortho-dichlorobenzene to produce a 4(di-substituted phenyl)-1-tetralone.

WO 95/15299 describes a process for the

preparation of (4S)-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone where racemic 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone is reduced using an asymmetric reagent to produce a mixture of cis and trans alcohols, said cis alcohols are separated from the trans alcohols and oxidized to the desired (4S) enantiomers.

In WO 98/15516 a process for producing 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone by reaction of o-dichloro-benzene and α -naphthol in the presence of a Fridel-Craft catalyst is described. From the reaction mixture the 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone is separated from another reaction product 4-(2,3-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone by a number of crystallisation steps.

A process for production of the (4S)-enantiomer of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone in a highly optical-pure form is described in WO 93/12062. In this process a 4-(3,4-dichlorophenyl)-4-ketobutanoic acid is first esterified with isopropylene or isobutylene. The ester is in three steps converted to isopropyl- or tert.-butyl- 4-(3,4-dichlorophenyl)-(4R)-phenylbutanoate which is cyclized in a final step to form the desired (4S)-4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone.

In spite of the several prior art processes discussed above, there is still a desire of improving the process for production of sertraline in order to make the process more cost efficient and more environmentally acceptable. In the process used industrially the overall yield of racemic sertraline from tetralone is only approximately 68-69% which means that approximately 30 % is lost in the process

and in one way or another forms a waste product that needs to be handled. In addition there is a wish to avoid the usage of titanium tetrachloride because of the difficulties of handling this compound and the
5 titanium containing waste that is formed during the process.

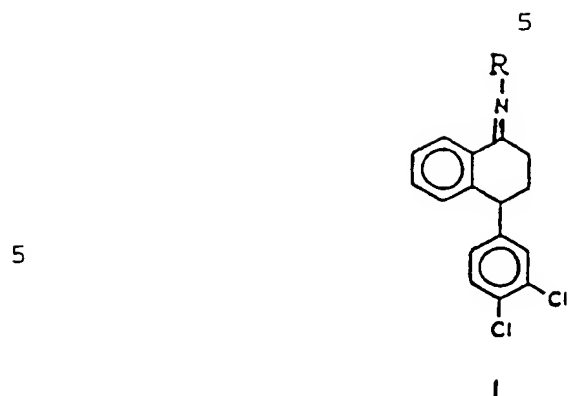
Thus it is an object of the present invention to provide a new process for producing racemic sertraline from tetralone in a simple, economical and
10 environmentally acceptable way.

SUMMARY OF THE INVENTION

15 The present invention is based on the recognition that the yield can be improved by ensuring that a higher cis/trans ratio is obtained, and that an advantageously high cis/trans ratio is favoured when the reduction of a compound formed by reaction of
20 tetralone and an amine contains a "bulky" substituent on the nitrogen atom instead of a small substituent such as a methyl group as used in the prior art. The required methyl substituent on the N-atom in the final product, sertraline, is added after the formation of
25 the desired conformation at the 1-carbon. Eventually the "bulky" group is removed.

Thus, in one aspect it is an object of the present invention to provide a process for the production of cis-(1S), (4S)-N-methyl-4-(3,4-dichloro-
30 phenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, sertraline, or a salt thereof, which process comprises the following steps:

35 i) the compound with the formula I



wherein R= a benzyl group, which may be substituted with one to three groups independently selected from: fluorine, chlorine, bromine, iodine, alkyl groups such as methyl, ethyl and propyl, and alkoxy groups such as methoxy, ethoxy, and propoxy,

15

is hydrogenated to obtain the compound with the formula II,



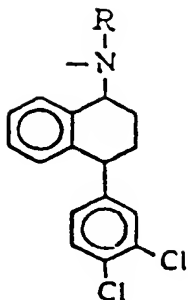
wherein R is as defined above,

30 ii) the compound with the formula II is reductively alkylated with formaldehyde or a derivative of formaldehyde or reacted with another methylating agent to obtain the compound with the formula III,

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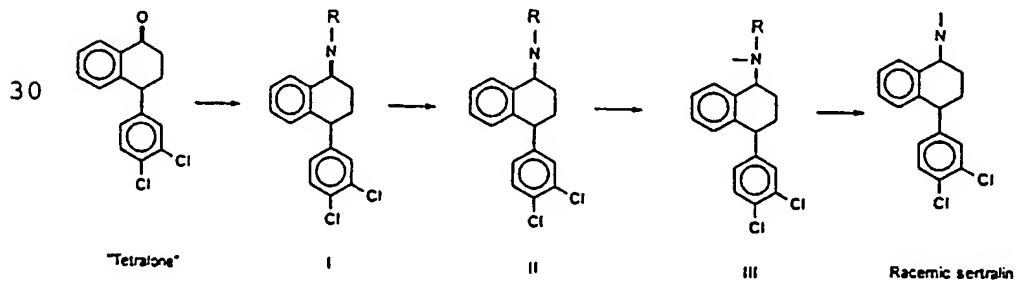
III

wherein R is as defined above, and

- iii) the compound with the formula III is converted to sertraline or a salt thereof, by removal of the group R.

Detailed explanation of the process of the invention for removing the group R from the compound (III) may be found below.

The compound (I) may be obtained by reaction of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone, tetralone, with $R-NH_2$ where R has the above meaning. This reaction may be performed without use of a catalyst especially without use of the environmentally hazardous titanium tetrachloride.



35

The compound of formula I, wherein R has the above significance is novel and in a further aspect of the invention forms part thereof.

The intermediate compound (II) may be obtained by
5 hydrogenation of a compound of the formula I.

Neither the compound (II) has been described previously and thus the invention in a still further aspect comprises the novel compound of formula II wherein R is as defined above.

10 The hydrogenation of compound (I) to compound (II) is preferably performed in the presence of a solid catalyst. In this step the configuration at the 1-carbon atom is determined.

The substituent on the nitrogen atom influences
15 the cis/trans ratio in the compound II, and a substituent as R favours a high cis/trans ratio compared to the ratio when a smaller substituent such as a methyl group is present in stead of R. The high cis/trans ratio is maintained in the subsequent two
20 steps for forming sertraline.

The compound (III) is manufactured by methylation of a compound of the formula (II), and eventually converted into sertraline by removal of the group R.

The methyl group introduced by the conversion of
25 compound II into the compound III remains attached to the nitrogen atom when the latter compound is converted into the desired compound, sertraline.

Neither the intermediate compound (III) wherein R has the above significance, has been previously
30 described and forms a further aspect of the invention.

Thus the present invention provides a process and intermediates for production of racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine in a surprisingly high yield when
35 calculated on the starting material compound (I) or

even "tetralone". This is because the cis/trans ratio for the reaction is very high and also because the conversion rate in the total process is high.

In addition the procedure is simple, inter alia because the conversion of (I) to (II) and (II) to (III) may be performed in one pot without the need for intermediate purification operations.

The process is gentle to the environment as it can be performed without the need for titanium tetrachloride. In addition it can be run cost efficiently as the yield is higher than the yield in previous known processes, the use of expensive compounds can be avoided, and excess $R-NH_2$ for the formation of (I), may be removed from the reaction mixture by distillation and reused.

DETAILED DESCRIPTION OF THE INVENTION

Conversion of "tetralone" to compound I

For the synthesis of sertraline the compound I may be formed by reacting 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone with an amine of the formula $R-NH_2$.

The reaction may be performed in any suitable solvent that is inert with respect to the reaction or it may be performed without a solvent. As water is produced during the reaction it is preferred to use a solvent that can remove the water by azeotropic distillation. Examples of such solvents are cyclohexane, benzene and toluene.

The temperature for the reaction can be selected between room temperature and the boiling temperature of the solvent. It is preferred to perform the reaction at a temperature in the interval 50-200°C, preferably between the boiling point of the azeotrope

of water and solvent and the boiling temperature of the solvent.

The reaction can be performed without any catalyst or can be performed with an acid catalyst
5 such as a carboxylic acid e.g. capronic acid. After the reaction is finished the solvent and excess amine may be removed by distillation and reused.

In connection with the group R the term "bulky" means that the group is large. Consequently the group
10 R may be selected among large groups that is substantially inert to the reaction in question. In this context large means that the group has a size substantially larger than the methyl group attached to the N-atom in prior art procedures. Usable groups R
15 according to this invention may be selected within the above definition.

As examples of groups R for use according to this invention can be mentioned: benzyl, o-chlorobenzyl, m-chlorobenzyl, p-chlorobenzyl, p-fluorobenzyl, 2,3-
20 dichlorobenzyl, 2,4-dichlorobenzyl, 2-bromo-4-chlorobenzyl, p-methoxybenzyl, 2,3-dimethoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2,3,5-trimethoxybenzyl, 4-ethylbenzyl.

In principle there are rather few limitations on
25 R, since the group is removed before the final product is achieved. However it is preferred to select R so that $R-NH_2$ has a convenient boiling point, i.e. it is not distilled off during reaction but can easily be removed by distillation after the reaction.

30 For industrial purposes it is preferred to use a compound that is available at a low price. For this reason it is preferred to use benzylamine which is both quite reactive and very cheap, and gives N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-
35 naphthalenyldene]-benzylamine as high melting

crystals in a surprisingly high yield.

Conversion of compound I to compound II

The reduction of compound I to compound II is
5 believed to be the step that determines the cis/trans
ratio for the final product.

The reduction may take place in several ways as
it will be known to the person skilled in the art. The
reduction may be performed using complex hydrides
10 (e.g. NaBH_4) or by hydrogenation. Reduction performed
by catalytic hydrogenation tends to give better
selectivity than reduction using the complex hydrides.
For example aliquots of N-[4-(3,4-dichlorophenyl)-3,4-
dihydro-1(2H)-naphthalenylidene]-benzylamine were
15 reduced with NaBH_4 and Raney nickel/ H_2 respectively,
and subsequently reductively alkylated with
formaldehyde, where after the cis/trans ratio was
analyzed. The result was a ratio of 53,8/46,2 using
 NaBH_4 compared to 82,9/17,1 for Raney Nickel/ H_2 which
20 clearly demonstrates the selectivity of the catalytic
hydrogenation. An even higher selectivity with a
cis/trans ratio of 93,5/6,5 has been observed using
palladium on carbon.

For the purpose of this invention the catalytic
25 hydrogenations can be performed using a solid catalyst
as known within the art, such as palladium on carbon,
rhodium on carbon and Raney nickel. The reaction can
be performed in any solvent that is inert to the
reaction e.g. ethanol. As it will be known within the
30 art hydrogenations using H_2 in the presence of a solid
catalyst gives varying results depending on the actual
used catalyst, particle size, pressure, temperature
etc. It is within the capabilities of the skilled
person in the art to determine which conditions gives
35 the optimal result in each actual reaction.

Conversion of compound II to III

The conversion of II to III is conveniently carried out in the same pot as the reaction of I to
5 II.

The reaction takes place simply by addition of a solution of formaldehyde to the reaction mixture from the previous step. The reaction takes place almost instantaneously and is almost quantitative.

10 In stead of formaldehyde, any derivative of formaldehyde such as paraformaldehyde, and acetals and hemiacetals thereof may be used.

The compound III may also be made by alkylation of compound II by conventional alkylation using for
15 example methyl iodide. The reaction is fast and high yielding but requires the isolation of the starting material which may be considered inconvenient.

As in the previous step any solvent that is inert to the reaction may be used.

20

Conversion of compound III to racemic Sertraline

When the compound III has been made it is converted to racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine
25 by removal of the group R according to the invention using any procedure known within the art, see for example Theodora W.Greene and Peter G.M. Wuts: Protective Groups in Organic Synthesis. 2. ed, p.364-366, John Wiley & sons, inc. 1991).

30 Thus for the use within this invention removal can e.g. be performed by hydrogenation in acidic environment or by treatment with an acid. Hydrogenation is preferred because R groups suitable for acid cleavage like for instance triphenylmethyl,
35 5-benzosuberyl, di(4-methoxyphenyl)methyl, 3,4-

dimethylbenzyl are all very expensive to introduce compared to the simple benzyl group. Hydrogenation may take place in a inert solvent such as ethanol, in the presence of a solid catalyst and an acid, such as
5 acetic acid or hydrochloric acid. Thus performing the debenzylation of N-benzyl-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-dihydro-1-naphthaleneamine in ethanol with acetic acid leads to about 80% of the cis and trans sertraline racemates and about 20 % of the
10 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-naphthalene.

The use of hydrochloric acid results in precipitation of the formed racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine as a hydrochloride which leads to an
15 almost complete conversion of the compound III to racemic sertraline hydrochloride. Surprisingly, the precipitation of the cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride does not influence the hydrogenation in
20 a negative way indicating that no clotting of the catalyst occurs.

Conversion of racemic sertraline to sertraline

The formed racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine
25 is separated from the reaction mixture using known procedures, such as crystallisation of cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine as a hydrochloride by addition of
30 hydrochloric acid followed by filtration of the crystals from the mixture.

In case that hydrochloride was used in the previous step and racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine
35 is present in form of a precipitate, the precipitate

and the solid catalyst are removed from the solution e.g. by filtration.

The purified racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride may be resolved by known procedures such as a diastereomeric crystallisation with D-(-)-mandelic acid, and subsequent conversion to the hydrochloride to produce the pharmaceutical desired form cis-(1S), (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride, sertraline hydrochloride.

The following examples are provided to illustrate the invention, not to be limiting in any way.

15

EXAMPLES

Example 1.

N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]benzylamine, (Formula I, R=Benzyl).

4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone ("tetralone") (100.0 g, 0.343 mole) and benzylamine (70.0 g, 0.653 mole) was refluxed in 200 ml toluene using a Dean-Stark water separator. When the theoretical amount of water (6.2) ml was trapped (7 hours), toluene and the excess benzylamine was distilled off in vacuo at 90°C. 250 ml 2-propanol was added and the suspension was heated to reflux. The solution was cooled to 5°C and stirred for 12 hours whereby crystals were formed. N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]benzylamine was removed by filtration and washed with 100 ml of cold 2-propanol and dried in vacuo, leaving 124.7 g (96 %) of N-[(3,4-

dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-benzylamine as light brown crystals.

Melting point: 102-103°C

¹H-NMR (CDCl₃, 300 MHz) δ ppm: 8.40 (m, 1H); 7.30 (m, 9H); 6.88 (m, 2H); 4.68 (s, 2H); 4.15 (m, 1H); 2.60 (t, 2H); 2.25 (m, 1H); 2.15 (m, 1H).

Example 2.

N-methyl-N-benzyl-4-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine,
(Formula III, R=benzyl).

A one litre autoclave was charged with N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-benzylamine (50.0 g, 0.132 mole), 10 ml triethylamine, 500 ml ethanol and 7.0 g Raney-nickel (BK 111 W, Degussa) washed dry with ethanol. The suspension was hydrogenated at a pressure of 3 bar at 60 °C until hydrogen uptake ceased (3 hours). A sample of the solution was analyzed using HPLC on a nucleosil C18 column, eluted using MeOH/phosphate buffer, pH 7.0 (9/1) with a flow of 0.9 ml/min and UV detection at 230 nm. A single product with a Rt=11.8 min was observed.

The synthesis was continued by addition of 25 ml of 37 % formaldehyde to the solution and hydrogenation at a pressure of 3 bar at 60°C was resumed. When hydrogen uptake ceased the hot solution was filtered and evaporated in vacuo to approximately 150 ml. 150 ml of toluene and 150 ml of water was added and the organic layer was isolated. The aqueous phase was extracted with 100 ml of toluene and the organic layers were combined and washed with 50 ml of water and evaporated in vacuo leaving 54.1 g of a light brown oil. HPLC analysis (nucleosil C18 column eluted using MeCN/phosphate buffer, pH 3.0 (1/1) with a flow

of 1.9 ml/min and UV detection at 230 nm) revealed two products with $R_t=14.53$ min (cis racemate: 82.9%) and $R_t=12.85$ min (trans racemate: 17.1 %).

5 **Example 3.**

N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, (cis-racemate, racemic sertraline).

A one litre autoclave was charged with 54.1 g (0,132 mole) of the light brown oil from example 2,
10 400 ml of ethanol, 14 ml (0,168 mole) of concentrated hydrochloric acid and 2.5 g of palladium on carbon 10 %. The suspension was hydrogenated at a pressure of 3 bar at room temperature until hydrogen uptake ceased (5 hours). The resulting grey suspension of
15 precipitated cis-racemate and catalyst was made alkaline with concentrated NaOH (20.0 ml; 0.22 mole), toluene was added and the mixture was stirred for 30 minutes. HPLC analysis (nucleosil C18 column eluted using MeOH/phosphate buffer, pH 7.0 (9/1) with a flow
20 of 0.7 ml/min and UV detection at 230 nm) revealed two products with $RT= 14.01$ min (cis-racemate) and $RT= 16.36$ min (trans-racemate) where the cis/trans ratio was 80.4/19.8. The catalyst was removed by filtration and toluene (200 ml) and water (600 ml) was added to
25 the filtrate. The organic layer was separated and the aqueous layer washed with toluene (100 ml).

The combined organic extracts were washed with water (40 ml) and brine (20 ml) and the solvent was evaporated in vacuo leaving 47.5 g of a light brown
30 oil. The oil was taken up in ethanol (250 ml), 25 ml of 6.28 M hydrochloric acid (0.157 mole) in ethanol was added and the solution was stirred for 3 hours at 0°C. The cis racemate immediately crystallized. The white solid was separated by filtration, washed with
35 80 ml of ethanol at -10°C and dried in vacuo at 50°C

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over night leaving 36.1 g of cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine as a white solid having a melting point of 288-290°C (uncorr.). The yield was calculated to 80.2% based on
5 N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-benzylamine. The overall yield based on tetralone was 77.0 %.

Example 4

10 N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-4-chlorobenzylamine,
(Formula I, R=p-chlorobenzyl)

4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone ("tetralone") was reacted with p-
15 chlorobenzyl amine according to the procedure outlined in example 1, and N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-4-chlorobenzylamine was obtained as brown crystals melting at 116-117°C, in a yield of 89.4 %.

20

Example 5

N-[4-(3,4-dichlorophenyl)-3,4-dihydro-naphthalenylidene]-4-methoxybenzylamine, (Formula I, R=p-methoxybenzyl)

25 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone ("tetralone") was reacted with p-methoxybenzyl amine according to the procedure outlined in example 1, and N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-4-methoxy-
30 benzylamine was obtained as brown crystals melting at 107-108°C, in an yield of 85.6 %.

35

Example 6

N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-3,4-dimethoxy-benzylamine, (Formula I, R=3,4-dimethoxy-benzyl).

5 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone ("tetralone") was reacted with 3,4-dimethoxy-benzyl amine according to the procedure outlined in example 1, and N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-3,4-dimethoxy-
10 benzylamine was obtained as colourless crystals melting at 121-122°C in an yield of 92.3 %.

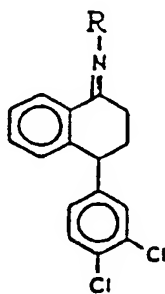
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P A T E N T C L A I M S

1. Process for the production of cis-(1S), (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, sertraline, or a salt thereof
5 c h a r a c t e r i z e d in that the process comprises the following steps:

i) the compound with the formula I

10



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I

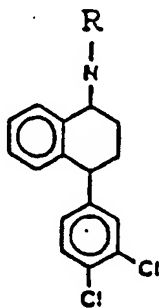
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wherein R= a benzyl group, which may be substituted with one to three groups independently selected from: fluorine, chlorine, bromine, iodine, alkyl groups such as methyl, ethyl and propyl, and alkoxy groups such as methoxy, ethoxy, and propoxy,

25

is hydrogenated to obtain the compound with the formula II

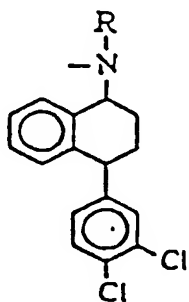
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II

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- ii) the compound with the formula II is reductively alkylated with formaldehyde or a derivative of formaldehyde or reacted with another methylating agent to obtain the compound with the formula III



III

- iii) the compound with the formula III is converted to sertraline or a salt thereof by removal of the group R.
2. Process according to claim 1, wherein step i) is performed in the presence of a catalyst selected from palladium on carbon, rhodium on carbon and Raney nickel.
3. Process according to claim 1 or 2, wherein step i) and step ii) are performed in the same pot without intermediate purification.
4. Process according to any of claims 1-3, wherein step iii) is performed by hydrogenolysis.
5. Process according to any of claims 1-4, wherein R= benzyl.
6. An N-substituted N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-amine of the formula I, wherein R is defined in claim 1.

7. An N-substituted N-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine of the formula II, wherein R is defined in claim 1.

8. An N-substituted N-methyl-4-(3,4-dichloro-5 phenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine of the formula III, wherein R is defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 00/00586

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C209/62 C07C209/26 C07C209/70 C07C211/42 C07C251/20		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) CHEM ABS Data, BEILSTEIN Data, PAJ, WPI Data, EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 947 499 A (CATALYS) 6 October 1999 (1999-10-06) claims	1
A	WO 93 01161 A (PFIZER LTD ;PFIZER (US)) 21 January 1993 (1993-01-21) cited in the application page 12; claims	1
A	US 4 536 518 A (WELCH JR WILLARD M ET AL) 20 August 1985 (1985-08-20)	
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">9 February 2001</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">16/02/2001</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Pauwels, G</div>

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